Palbociclib in Combination with Chemotherapy in Pediatric and Young Adult Patients with Relapsed/Refractory Acute Lymphoblastic Leukemia and Lymphoma: A Children’s Oncology Group Study (AINV18P1)

Elizabeth Raetz¹, David T. Teachey², Charles Minard³, Xiaowei Liu⁴, Robin Norris⁵, Kristina Z. Denic⁶, Joel Reid⁶, Nikki Evensen¹, Lia Gore⁷, Elizabeth Fox⁸, Mignon Loh⁹, Brenda Weigel¹⁰, and William Carroll¹

1NYU Langone Health
2The Children’s Hospital of Philadelphia Center for Childhood Cancer Research
3Baylor College of Medicine
4Children’s Oncology Group
5Cincinnati Children’s Hospital Medical Center Cancer and Blood Diseases Institute
6Mayo Clinic Department of Oncology
7UC Health University of Colorado Hospital
8St Jude Children’s Research Hospital Department of Oncology
9University of Washington
10University of Minnesota Masonic Cancer Center

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Abstract

Background Cyclin D has been shown to play an essential role in acute lymphoblastic leukemia (ALL) initiation and progression, providing rationale for targeting the CDK4/6-cyclin D complex that regulates cell cycle progression. Procedure The Children’s Oncology Group AINV18P1 phase 1 trial evaluated the CDK4/6 inhibitor, palbociclib, in combination with standard four-drug reinduction chemotherapy in children and young adults with relapsed/refractory B- and T-cell lymphoblastic leukemia (ALL) and lymphoma. Palbociclib (50 mg/m²/dose) was administered orally once daily for 21 consecutive days, first as a single agent (days 1-3) and subsequently combined with reinduction chemotherapy. This two-part study was designed to determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) followed by an expansion pharmacokinetic (PK) cohort. Results Twelve heavily pretreated patients enrolled, all of whom were evaluable for toxicity. One dose-limiting hematologic toxicity (DLT) occurred at the starting dose of 50 mg/m²/dose orally for 21 days. No additional DLTs were observed in the dose determination or PK expansion cohorts and overall rates of grade 3/4 non-hematologic toxicities were comparable to those observed with the chemotherapy platform alone. Five complete responses were observed, two among four patients with T-ALL and three among seven patients with B-ALL. Pharmacokinetic studies showed similar profiles with both liquid and capsule formulations of palbociclib. Conclusions Palbociclib in combination with reinduction chemotherapy was well tolerated with a RP2D of 50 mg/m²/day for 21 days. Complete responses were observed among heavily pretreated patients.

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patients-with-relapsed-refractory-acute-lymphoblastic-leukemia-and-lymphoma-a-childrens-oncology-group-study-ainv18p1

Figure 1

A. Secondary Outcome Measures for Patient Samples

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Disease Status</th>
<th>Response</th>
<th>WBC (10^9/L)</th>
<th>CD38 (% of cells)</th>
<th>pCR (size of cells)</th>
<th>CD123-MFI Unstained MFI</th>
<th>CD45-MFI Unstained MFI</th>
<th>CD95-MFI Unstained MFI</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>B-ALL (B1)</td>
<td>PR</td>
<td>23.89%</td>
<td>30.99%</td>
<td>3.25</td>
<td>5.21</td>
<td>1.45</td>
<td>2.32</td>
</tr>
<tr>
<td>#2</td>
<td>T-ALL (B1)</td>
<td>CR</td>
<td>12.32%</td>
<td>0.93%</td>
<td>3.17</td>
<td>5.94</td>
<td>1.68</td>
<td>2.37</td>
</tr>
<tr>
<td>#3</td>
<td>T-ALL (B2)</td>
<td>CR</td>
<td>32.17%</td>
<td>20.75%</td>
<td>3.33%</td>
<td>6.67%</td>
<td>15.56%</td>
<td>15.68%</td>
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<tr>
<td>#4</td>
<td>T-ALL (B1)</td>
<td>OR</td>
<td>0.85%</td>
<td>0.04%</td>
<td>10.99%</td>
<td>1.47%</td>
<td>23.85%</td>
<td>23.12%</td>
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<tr>
<td>#5</td>
<td>T-ALL (B1)</td>
<td>CR</td>
<td>8.75%</td>
<td>0%</td>
<td>10%</td>
<td>21.57%</td>
<td>19.19%</td>
<td>21.54%</td>
</tr>
</tbody>
</table>

Supplemental Figure 1

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